

# SEQUENCE LISTING

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<120> CONJUGATES COMPRISING HUMAN IL-18 AND  
 SUBSTITUTION MUTANTS THEREOF

<130> PU60053

<140> TO BE ASSIGNED

<141> 2004-04-14

<150> 60/462,947

<151> 2003-04-15

<160> 28

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 157

<212> PRT

<213> Homo sapiens

<400> 1

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Phe | Gly | Lys | Leu | Glu | Ser | Lys | Leu | Ser | Val | Ile | Arg | Asn | Leu | Asn |
| 1   |     |     |     | 5   |     |     |     |     |     | 10  |     |     |     |     | 15  |
| Asp | Gln | Val | Leu | Phe | Ile | Asp | Gln | Gly | Asn | Arg | Pro | Leu | Phe | Glu | Asp |
|     |     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |
| Met | Thr | Asp | Ser | Asp | Cys | Arg | Asp | Asn | Ala | Pro | Arg | Thr | Ile | Phe | Ile |
|     |     | 35  |     |     |     |     |     | 40  |     |     |     |     | 45  |     |     |
| Ile | Ser | Met | Tyr | Lys | Asp | Ser | Gln | Pro | Arg | Gly | Met | Ala | Val | Thr | Ile |

|   |     |     |     |     |
|---|-----|-----|-----|-----|
| 50  |     | 55  |     | 60  |
| Ser Val Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile |     |     |     |     |
| 65  |     | 70  |     | 75  |
| Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys |     |     |     |     |
|   | 85  |     | 90  |     |
| Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys |     |     |     |     |
|   | 100 |     | 105 |     |
| Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu |     |     |     |     |
|   | 115 |     | 120 |     |
| Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu |     |     |     |     |
|   | 130 |     | 135 |     |
| Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp             |     |     |     |     |
| 145   |     | 150 |     | 155 |

<210> 2

<211> 157

<212> PRT

<213> Mus musculus

<400> 2

|   |     |    |     |    |
|---|-----|----|-----|----|
| Asn Phe Gly Arg Leu His Cys Thr Thr Ala Val Ile Arg Asn Ile Asn |     |    |     |    |
| 1   |     | 5  |     | 10 |
| Asp Gln Val Leu Phe Val Asp Lys Arg Gln Pro Val Phe Glu Asp Met |     |    |     |    |
|   | 20  |    | 25  |    |
| Thr Asp Ile Asp Gln Ser Ala Ser Glu Pro Gln Thr Arg Leu Ile Ile |     |    |     |    |
|   | 35  |    | 40  |    |
| Tyr Met Tyr Lys Asp Ser Glu Val Arg Gly Leu Ala Val Thr Leu Ser |     |    |     |    |
|   | 50  |    | 55  |    |
| Val Lys Asp Ser Lys Met Ser Thr Leu Ser Cys Lys Asn Lys Ile Ile |     |    |     |    |
| 65  |     | 70 |     | 75 |
| Ser Phe Glu Glu Met Asp Pro Pro Glu Asn Ile Asp Asp Ile Gln Ser |     |    |     |    |
|   | 85  |    | 90  |    |
| Asp Leu Ile Phe Phe Gln Lys Arg Val Pro Gly His Asn Lys Met Glu |     |    |     |    |
|   | 100 |    | 105 |    |
| Phe Glu Ser Ser Leu Tyr Glu Gly His Phe Leu Ala Cys Gln Lys Glu |     |    |     |    |
|   | 115 |    | 120 |    |
| Asp Asp Ala Phe Lys Leu Ile Leu Lys Lys Lys Asp Glu Asn Gly Asp |     |    |     |    |
|   | 130 |    | 135 |    |
| Lys Ser Val Met Phe Thr Leu Thr Asn Leu His Gln Ser             |     |    |     |    |

145

150

155

&lt;210&gt; 3

&lt;211&gt; 203

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 3

```

Met His His His His His His Thr Arg Gly Met Ala Ala Glu Pro Val
 1           5           10           15
Glu Asp Asn Cys Ile Asn Phe Val Ala Met Lys Phe Ile Asp Asn Thr
          20           25           30
Leu Tyr Phe Ile Ala Glu Asp Asp Glu Asn Leu Glu Ser Asp Tyr Phe
        35           40           45
Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn Asp Gln
        50           55           60
Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp Met Thr
65           70           75           80
Asp Ser Asp Cys Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile Ile Ser
          85           90           95
Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile Ser Val
          100          105          110
Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile Ile Ser
          115          120          125
Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys Ser Asp
          130          135          140
Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys Met Gln
145           150           155           160
Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu Lys Glu
          165          170          175
Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu Gly Asp
          180          185          190
Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
          195          200

```

&lt;210&gt; 4

&lt;211&gt; 157

&lt;212&gt; PRT

<213> Artificial Sequence

<220>

<223> Whereby the Cysteine at position 38 of the human  
IL-18 sequence has been replaced with Serine.

<400> 4

```
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
 1             5             10             15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
      20             25             30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
      35             40             45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
      50             55             60
Ser Val Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile
      65             70             75             80
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys
      85             90             95
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys
      100            105            110
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
      115            120            125
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu
      130            135            140
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
      145            150            155
```

<210> 5

<211> 157

<212> PRT

<213> Artificial Sequence

<220>

<223> Whereby the Cysteine at position 38 of the human  
IL-18 sequence has been replaced with Serine, the  
Cysteine at position 68 has been replaced with  
Aspartic acid, and the Asparagine at position 78  
has been replaced with Cysteine.

<400> 5

```
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
 1           5           10           15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
          20           25           30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
      35           40           45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
      50           55           60
Ser Val Lys Asp Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile
65           70           75           80
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys
          85           90           95
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys
      100           105           110
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
      115           120           125
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu
      130           135           140
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
145           150           155
```

<210> 6

<211> 157

<212> PRT

<213> Artificial Sequence

<220>

<223> Whereby the Cysteine at position 38 of the human  
IL-18 sequence has been replaced with Serine, the  
Cysteine at position 68 has been replaced with  
Aspartic acid, and the Glutamic acid at position  
121 has been replaced with Cysteine.

<400> 6

```
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
 1           5           10           15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
```





|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|     | 100 |     | 105 |     | 110 |     |     |     |     |     |     |     |     |     |     |
| Met | Gln | Phe | Glu | Ser | Ser | Ser | Tyr | Glu | Gly | Tyr | Phe | Leu | Ala | Cys | Glu |
|     | 115 |     | 120 |     | 125 |     |     |     |     |     |     |     |     |     |     |
| Lys | Glu | Arg | Asp | Leu | Phe | Lys | Leu | Ile | Leu | Lys | Lys | Glu | Asp | Glu | Leu |
|     | 130 |     | 135 |     | 140 |     |     |     |     |     |     |     |     |     |     |
| Gly | Asp | Arg | Ser | Ile | Met | Phe | Thr | Val | Gln | Asn | Glu | Cys |     |     |     |
| 145 |     |     | 150 |     | 155 |     |     |     |     |     |     |     |     |     |     |

<210> 9

<211> 157

<212> PRT

<213> Artificial Sequence

<220>

<223> Whereby the Cysteine at position 38 of the human IL-18 sequence has been replaced with Serine, the Cysteine at position 68 has been replaced with Serine, and Leucine at position 144 has been replaced with Cysteine.

<400> 9

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Phe | Gly | Lys | Leu | Glu | Ser | Lys | Leu | Ser | Val | Ile | Arg | Asn | Leu | Asn |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Asp | Gln | Val | Leu | Phe | Ile | Asp | Gln | Gly | Asn | Arg | Pro | Leu | Phe | Glu | Asp |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |
| Met | Thr | Asp | Ser | Asp | Ser | Arg | Asp | Asn | Ala | Pro | Arg | Thr | Ile | Phe | Ile |
|     |     | 35  |     |     |     | 40  |     |     |     |     |     | 45  |     |     |     |
| Ile | Ser | Met | Tyr | Lys | Asp | Ser | Gln | Pro | Arg | Gly | Met | Ala | Val | Thr | Ile |
|     | 50  |     |     |     | 55  |     |     |     | 60  |     |     |     |     |     |     |
| Ser | Val | Lys | Ser | Glu | Lys | Ile | Ser | Thr | Leu | Ser | Cys | Glu | Asn | Lys | Ile |
| 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |     |
| Ile | Ser | Phe | Lys | Glu | Met | Asn | Pro | Pro | Asp | Asn | Ile | Lys | Asp | Thr | Lys |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |     |
| Ser | Asp | Ile | Ile | Phe | Phe | Gln | Arg | Ser | Val | Pro | Gly | His | Asp | Asn | Lys |
|     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |
| Met | Gln | Phe | Glu | Ser | Ser | Ser | Tyr | Glu | Gly | Tyr | Phe | Leu | Ala | Cys | Glu |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Lys | Glu | Arg | Asp | Leu | Phe | Lys | Leu | Ile | Leu | Lys | Lys | Glu | Asp | Glu | Cys |
|     | 130 |     |     |     |     | 135 |     |     |     |     |     | 140 |     |     |     |



Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp  
145 150 155

<210> 10

<211> 157

<212> PRT

<213> Artificial Sequence

<220>

<223> Whereby the Cysteine at position 38 of the human  
IL-18 sequence has been replaced with Serine, the  
Cysteine at position 68 has been replaced with  
Serine, and Aspartic acid at position 157 has been  
replaced with Cysteine.

<400> 10

Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn  
1 5 10 15  
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp  
20 25 30  
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile  
35 40 45  
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile  
50 55 60  
Ser Val Lys Ser Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile  
65 70 75 80  
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys  
85 90 95  
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys  
100 105 110  
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu  
115 120 125  
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu  
130 135 140  
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Cys  
145 150 155

<210> 11

<211> 4  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 11  
Tyr Phe Gly Lys  
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<210> 12  
<211> 4  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 12  
Leu Glu Ser Lys  
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<210> 13  
<211> 5  
<212> PRT  
<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 13

Leu Ser Val Ile Arg

1 5

<210> 14

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 14

Asn Leu Asn Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu

1 5 10 15

Phe Glu Asp Met Thr Asp Ser Asp Cys Arg

20 25

<210> 15

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 15

Asp Asn Ala Pro Arg

1 5

<210> 16

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 16

Thr Ile Phe Ile Ile Ser Met Tyr Lys

1 5

<210> 17

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 17

Asp Ser Gln Pro Arg

1 5

<210> 18

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 18

Gly Met Ala Val Thr Ile Ser Val Lys

1 5

<210> 19

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 19

Ile Ser Thr Leu Ser Cys Glu Asn Lys

1

5

<210> 20

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 20

Ile Ile Ser Phe Lys

1

5

<210> 21

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 21

Glu Met Asn Pro Pro Asp Asn Ile Lys

1

5

<210> 22

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 22

Ser Asp Ile Ile Phe Phe Gln Arg

1

5

<210> 23

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 23

Ser Val Pro Gly His Asp Asn Lys

1

5

<210> 24

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 24

Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu  
1 5 10 15  
Lys

<210> 25

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 25

Asp Leu Phe Lys  
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<210> 26

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 26

Leu Ile Leu Lys

1

<210> 27

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 27

Glu Asp Glu Leu Gly Asp Arg

1

5

<210> 28

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated  
wild type IL-18

<400> 28

Ser Ile Met Phe Thr Val Gln Asn Glu Asp

1

5

10